REMARKS

Claims 1, 5-13, 15-21, and 23-24 are pending in this application. Claims 15-21 were previously withdrawn from consideration by the Examiner and claims 2-4, 14, and 22 were previously cancelled.

Claims 1 and 13 have been amended. Support for these amendments can be found, for example, at pages 3-4 and 10 of the specification. Accordingly, these amendments raise no new matter issues.

Applicant acknowledges and appreciates the withdrawal of the claim objections and the previous rejections under 35 U.S.C. § 112, first and second paragraphs, for the reasons set forth in the Office Action dated August 15, 2006.

I. Rejection under 35 U.S.C. § 112, ¶ 2

The Examiner has rejected claims 1 and 5-12 under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite "because the claims lack an essential step in the method of preparing a polyanion of cyclosporin." [Aug. 15, 2006, Office Action at 3]. According to the Examiner, "[t]he omitted step is the outcome of the process, it is not clear whether the polyanion is obtained or not." [*Id.*]. Claims 5-12 were rejected for being dependent on a rejected claim. Applicant respectfully traverses this rejection.

Applicant respectfully submits that one skilled in the art reading claim 1 would understand that the outcome of the claimed process is the production of polyanion of formula (II) as defined in the claim. Specifically, claim 1 is directed to a "process for preparing a *polyanion* . . . wherein said *polyanion* has the formula [(II)]." Moreover, the specification explains that the polyanion "*obtained*" has the formula (II). [Specification at

3-4; *see also* page 10 ("The polyanions of general formula (II) resulting from the process according to the invention are useful as intermediates in the preparation of cyclosporin derivatives . . . .")]. Thus, the plain language of the claim coupled with the disclosure of the present specification, would allow the skilled artisan to readily understand that the outcome of the claimed process is the polyanion of formula (II) as defined in claim 1.

In order to expedite prosecution, however, Applicant has amended claim 1 to insert the language "to form said polyanion." Applicant submits that this amendment does not alter the scope of claim 1 in any way; rather, this amendment merely makes explicit that which was at least implicit. This amendment obviates the Examiner's rejection and Applicant respectfully requests that the Examiner withdraw this rejection.

II. Rejection under 35 U.S.C. § 103

The Examiner has rejected claims 13, 23, and 24 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Barriere et al. (U.S. Patent No. 5,994,299) in view of Seebach et al. (Helvetica Chemica Acta 76, 1564-1590 (1993)) and Gordon et al. (U.S. Patent No. 5,559,256. [Aug. 15, 2006, Office Action at 3].

According to the Examiner, Barriere et al. discloses that activation of sarcosine at the 3-position of the cyclosporin of formula (II) can be carried out with an organometallic derivative, such as a lithium derivative, which can be n-butyllithium, lithium diisopropylamide, or a mixture of the two. [*Id.*]. The Examiner concedes, however, that Barriere et al. "do not teach the use of a hexamethyldisilazane metal salt to activate the cyclosporine [sic] of formula (II) to form a polyanion." [*Id.* at 4]. The Examiner posits that Seebach et al. allegedly "disclose an enolate of cyclosporine A including sarcosine

enolate can be formed with cyclosporine A is treated with lithium diisopropylamide (LDA), where the deprotonation at sarcosine occurs, and the alkylation product can be detected after reacting with an alkylating agent . . . ." [*Id.*]. Gordon et al., according to the Examiner, "disclose the protected amino ester LXVIII can be alkylated via its enolate anion, which is formed by treatment of the ester with a base such as lithiumdisoporpylamide [sic], lithium bis(trimethylsilyl)amide (another name for hexamethyldisilazane lithium salt, see attached STN search result) or the like to give LXIX . . . ." [*Id.*]. The Examiner concludes that it would have allegedly been obvious "to combine the three references to prepare a [4'-hydroxy-MeLeu]^4-cyclosporin compound of general formula (I) via a polyanion intermediate as indicated by Barrier et al. using either hexamethyldisilazane lithium salt or lithiumdisoporpylamide [sic] to make the cyclosporin polyanion intermediate (claim 13) because both reagents are strong base [sic] and can deprotonate the sarcosine present on the cyclosporin to form an enolate anion, which is then reacting with an alkylating agent to form a cyclosporine [sic] derivative." [*Id.*]. Applicants respectfully traverse this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness. For example, there is nothing in the three references that contain some suggestion or incentive that would have motivated the skilled artisan to combine the references to prepare the claimed cyclosporin derivative substituted at the 3-position of claim 13 via a polyanion intermediate using a hexamethyldisilazane lithium salt at the specified reaction conditions, including, for example, temperature conditions ranging from -40°C to 0°C. Specifically, nothing in the combined teachings of these references leads the

skilled artisan to use the process of the present invention under the conditions specified in the claims, for the reasons described below.

Barriere et al. describes the synthesis of certain 3-substituted cyclosporin derivatives using lithium diisopropylamide at temperatures from -70°C to -78°C. [*See* Barriere et al., Example 1, col. 7:63 – col. 8:10]. Seebach et al. also discloses the generation of a cyclosporin polyanion, where the reaction is performed using tetrahydrofuran as solvent at a temperature of -75°C or -78°C. [*See* Seebach et al., page 1565, Scheme 1; page 1566, Scheme 2]. Therefore, the combined teaching of Barriere et al. and Seebach et al. fails to lead the skilled artisan to either the reactant of the present invention or the reaction conditions, including, for example, temperature conditions ranging from -40°C to 0°C.

As noted by the Examiner, Gordon et al. discloses the possibility of forming an enolate using lithium bis(trimethylsilyl)amide. [*See* Gordon et al., col. 47:26-36]. Gordon et al., however, fails to disclose any examples of this reaction, nor are any reaction conditions mentioned, including, for example, temperature. Furthermore, the enolate in question, an ester of formula LXVIII (top of column 43), involves formation of an enolate in a non-cyclic system, not a cyclic structure as in the present case, and certainly not the specific undecapeptide cyclosporins of the claims. Moreover, Gordon et al. does not suggest the desirability to make a modification to the method for converting an ester of formula LXVIII to an ester of formula LXIX to arrive at the claimed method for preparing the cyclosporin polyanion intermediate of claim 13 through the use of hexamethyldisilazane lithium salt. *See In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995) ("Obviousness cannot be established by combining the teachings of the prior art

to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.").

For these reasons, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

In view of these remarks, Applicant respectfully requests reconsideration and reexamination of this application.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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